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Intranasal Interferon α2 for Prevention of Rhinovirus Infection and Illness

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In two placebo-controlled, double-blind studies, the prophylactic efficacy of recombinant DNA-produced interferon α2 (IFN-α2) against induced rhinovirus (RV) type 39 infection in susceptible volunteers was assessed. IFN-α2 was given by intranasal drops in either multiple treatments (11.4×10^6 IU four times per day for four days) or one treatment daily (42.8×10^6 IU once per day for five days) starting before RV type 39 challenge. The efficacy rates of multiple-dose IFN-α2 for preventing infection, virus shedding, and RV type 39–specific colds were 78%, 78%, and 100%, respectively. The corresponding rates for one daily treatment were 45%, 64%, and 75%, respectively. Both dosage regimens were associated with significant reductions in days of virus shedding and nasal mucus production. In the second study, three IFN-α2 recipients developed transient leukopenia (<4,000 leukocytes/mm³). The results suggest that intranasal IFN-α2 may prove to be a safe and effective method of preventing rhinovirus infection and illness.

Since their discovery, the human interferons (HuIFNs) have been important candidates for the prophylaxis and therapy of respiratory viral infections. In 1973, Merigan et al [1] demonstrated that frequent intranasal administration of human leukocyte-derived IFN (HuIFN-α) (14×10^6 IU over four days) was associated with a reduction in infection rates in volunteers challenged with rhinovirus (RV) type 4. Greenberg et al [2] observed only a modest effect on the severity of illness and on titers of virus in nasal secretions of RV type 13–challenged volunteers, when cotton pledgets soaked with HuIFN-α (10^6 IU) were placed intranasally in conjunction with oral administration of antihistamines. Scott et al [3] have reported that repetitive intranasal spraying of highly purified HuIFN-α in high dosages (90×10^6 IU over four days) had significant protective effect against illness but not against infection following challenge with an experimental strain of RV type 9. These authors also noted that administration of HuIFN-α to uninfected volunteers was associated with mild upper respiratory symptoms (stuffiness, sore throat, and epistaxis) in the majority of recipients [3].

Recently, recombinant DNA techniques have been successfully applied to the production of IFN from human genes in *Escherichia coli* [4–6]. In a preliminary communication, Scott et al [7] reported that repeated intranasal administration of IFN-α2 (90×10^6 IU over four days) was associated with significant reductions in the frequency of virus shedding and illness in volunteers challenged with RV type 9.

In the present studies, we evaluated the prophylactic efficacy of IFN-α2 against experimentally induced RV type 39 infections in susceptible volunteers. We sought to determine (*1*) whether repetitive prophylactic administration of IFN-α2 had demonstrable antiviral and clinical effects and (*2*) whether once-daily administration was a feasible alternative to a multiple-dose regimen.

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Written informed consent in a form approved by the University of Virginia Human Investigation Committee was obtained from all participants. The guidelines for human experimentation of the US Department of Health and Human Services and the University of Virginia were followed in conducting these studies.

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Materials and Methods

Study population. Fifty-five healthy adult volunteers were included in two separate studies (26 in the first, 29 in the second), after serum neutralizing antibody measurements indicated susceptibility (reciprocal titer, ≤2) to the challenge virus. Eight volunteers with a history of asthma and stable pulmonary function tests (whose forced vital capacity and forced expiratory volume in 1 sec were >80% that of predicted values [8]) were included in the second study. Individuals who had an upper respiratory illness or fever within two weeks or who were currently taking intranasal or oral medications (except theophyllines among asthmatics or oral contraceptives) were excluded from participation.

Subjects were housed individually in separate rooms from the day before virus challenge until five days after challenge.

Administration of IFN. IFN-$\alpha 2$ (study drug SCH30500; Schering Corp, Bloomfield, NJ) was provided as a lyophylized powder (specific activity, $10^{8.0}$ IU/mg of protein) containing 2 mg of human serum albumin/ml and phosphate buffers. Lyophylized albumin, identical in appearance and protein content, served as placebo. Drug was reconstituted each day prior to administration with distilled water (final pH, 7.2–7.4) and was administered by a member of the project staff with an Eppendorf® calibrated pipette (Brinkmann Instruments, Westbury, NJ).

For drug administration, volunteers were instructed to lie supine with their neck extended, so that the chin and external auditory meatus were aligned in a vertical plane [9]. The pipette tip was introduced ~1.5 cm into the nasal vestibule, and drug solution was delivered by drops (0.25 ml per nostril) over a 5-sec period. Subjects were instructed to maintain neck extension for 1 min, to remain supine for 10 min, and to avoid nose blowing for 30 min after drug administration. Each treatment consisted of two intranasal applications separated by an interval of 20–30 min (total volume, 1.0 ml per treatment).

In the first study, four treatments (11.4×10^6 IU per treatment) were given each day (9:00 AM, 2:00 PM, 7:00 PM, and 12:00 AM [midnight]) beginning 20 hr before virus challenge and continuing through the morning of the third postchallenge day. The daily and total IFN dosages were 45.5×10^6 IU and 182×10^6 IU, respectively. In the second study, one treatment (42.8×10^6 IU per treatment) was given each morning (at 9:00 AM), beginning two days prior to virus challenge and continuing through the second postchallenge day for a total dosage of 214×10^6 IU.

Virus challenge. A safety-tested pool of RV type 39, which was a clinical isolate passaged twice in WI-38 human embryonic lung fibroblasts (HEM Research, Rockville, Md), was used as the challenge virus [10]. The virus was administered twice by intranasal drops (0.25 ml per nostril) in the same manner as the study drugs. In the first study, a total of 21 $TCID_{50}$ was given 1 hr after the fourth and fifth doses of medication. In the second study, a total of 88 $TCID_{50}$ was given 1 and 6 hr after the third dose of medication.

Measures of infection. The rates of infection were determined by virus isolation and by measurements of homotypic serum neutralizing antibody titers on paired specimens obtained one or two days prior to virus challenge and three weeks later. Before and during the first through fifth days after challenge, nasal wash specimens were collected prior to drug administration for virus isolation by previously described methods [10, 11]. All specimens were processed in both plain collection broth and broth containing sheep antibody to IFN in a concentration sufficient to inhibit ~2,500 IU of IFN-$\alpha 2$/ml [11]. At least one virus isolate from each volunteer was identified as type 39 by neutralization with standard antiserum (National Institutes of Health, Bethesda, Md).

Serum neutralizing antibody titers against the challenge virus were measured by a standard tube neutralization method [12].

Measures of illness. The frequency and severity of clinical illness were determined by monitoring clinical symptoms and weighing expelled nasal secretions by previously described methods [10]. Symptom scores were performed by using a modification [12] of the method of Jackson et al [13]. Oral temperatures were measured twice daily (8:00–9:00 AM and 4:00–6:00 PM). In the second study forced vital capacity and forced expiratory volume (for 1 sec) were measured with a Stead-Wells spirometer (Warren E. Collins, Braintree, Mass) in all subjects to determine the base-line value and within 2 hr of a preceding treatment before virus challenge and on days 1, 3, and 4 after challenge.

Subjects were monitored for the occurrence of respiratory illness during the second week (days 6–12) after virus challenge by self-recording of

symptoms on a check list. The return rate of the check list was 83% in the first study and 82% in the second. An upper respiratory illness (URI) was considered to be present during the follow-up period if the subject reported nasal discharge with or without other respiratory symptoms on at least two consecutive days.

Measures of side effects. The subjects were questioned on the last day of drug administration about symptoms (nasal burning or irritation, sneezing, cough, choking, and runny nose) that occurred with or immediately after intranasal drug administration. Symptoms obtained at this time were not included in the daily symptom scores. Follow-up blood and urine specimens for toxicity monitoring were obtained at three days in the first study and at 24 hr in the second after the last dose of study medication. Serum samples were collected prior to and at three weeks following the study for measurement of serum neutralizing antibody to IFN-α2. These assays were performed on coded samples in the laboratory of the Pediatric Infectious Disease Unit, University of Utah School of Medicine, Salt Lake City.

IFN assays. IFN concentrations in nasal washes and sera were determined on coded samples by a previously described bioassay [14]. HuIFN-α standard G-023-901-527 (National Institutes of Health) (reported titer, 20,000 IU/ml) had a mean ± SD reciprocal titer of 16,724 ± 8,964 in six assays.

Analysis of data. The significance of differences in proportions were calculated by Fisher's exact test; differences in symptom scores, by Mann-Whitney *U* test; and differences in nasal mucus weights, by Student's *t*-test. In each instance, *P* values are those for two-tailed testing, and data are expressed as means ± SEM. Efficacy rates (percentages) were determined by the following calculation: (rate in placebo-treated patients − rate in IFN-treated patients)/(rate in placebo-treated patients) × 100.

All treatments, clinical evaluations, symptom analyses, and virologic studies were conducted under double-blind conditions.

Results

Study group. Three volunteers were excluded from the analysis of drug efficacy because of prechallenge serum neutralizing antibody titers of ≥4 (one placebo subject in each study) or prechallenge isolation of a wild-type rhinovirus (one IFN recipient in the first study). In the first study, the ratios of male to female subjects (mean age) were 7:5 (20.0 years) in the IFN group and 4:8 (21.7 years) in the placebo group. In the second study, the corresponding ratios were 10:4 (22.6 years) in the IFN group and 7:7 (20.9 years) in the placebo group. In the second study, four volunteers with stable asthma were randomized to IFN treatment and four to placebo.

Nasal IFN concentrations. The concentrations of IFN in nasal wash among IFN recipients are shown in figure 1 for both studies. None of the placebo or IFN recipients had nasal wash concentrations of >3 IU/ml prior to drug administration (one IFN recipient in the first study was not tested). In the first study, in which nasal washes were collected at 8–9 hr after a previous dose, the geometric mean IFN concentrations were 652, 780, 1,010, and 14 IU/ml in the IFN recipients on the first through fourth days after virus challenge.

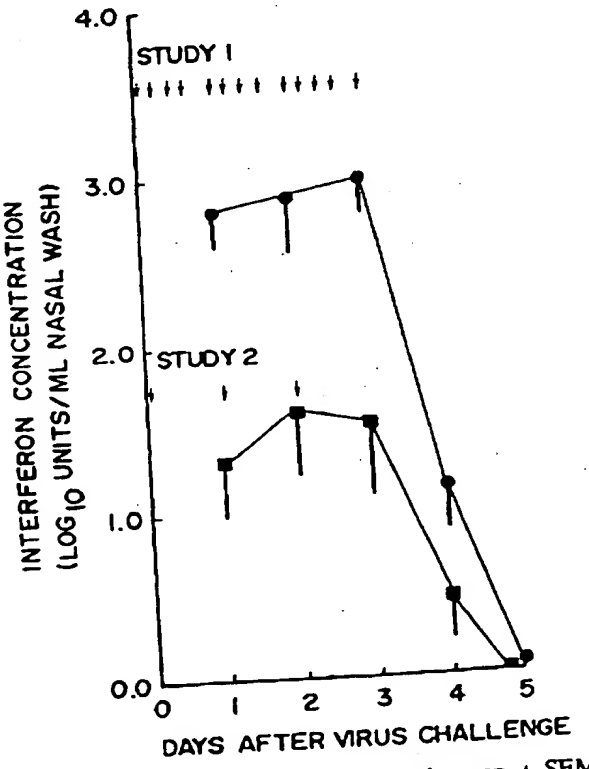

Figure 1. IFN concentrations (geometric mean ± SEM) in nasal wash samples of 12 IFN-treated volunteers in study 1 (●) and 14 in study 2 (■) expressed in $\log_{10}$ IU/ml of nasal wash. The times of IFN administration are indicated by arrows. The dose per treatment was 11.4×10^6 IU in study 1 and 42.8×10^6 IU in study 2.

Table 1. Infection rates and virus shedding following experimental intranasal exposure to RV type 39.

Study	Treatment	No. of subjects	No. shedding virus (%)	No. with seroconversion (%)	No. with infection (%)	No. of days of virus shedding/total days of observation (%)
1	Placebo	12	9 (75)*	4 (33)	9 (75)*	33/60 (55)†
	IFN	12	2 (17)*	0	2 (17)*	6/60 (10)†
2	Placebo	14	11 (79)‡	7 (50)	11 (79)	45/70 (64)†
	IFN	14	4 (29)‡	5 (36)	6 (43)	11/70 (16)†

NOTE. Seroconversion was defined as a fourfold or greater rise in serum homotypic neutralizing antibody to RV type 39 between prechallenge and convalescent-phase sera. Infection was defined as nasopharyngeal shedding of rhinovirus type 39 and/or seroconversion. The geometric mean ± SEM convalescent-phase antibody titer (log_2) in eight infected IFN recipients was 3.1 ± 0.8 and in 20 placebo recipients was 2.5 ± 0.4.

* $P < 0.02$ (placebo vs IFN group).

† $P < 10^{-4}$ (placebo vs IFN group).

‡ $P < 0.03$ (placebo vs IFN group).

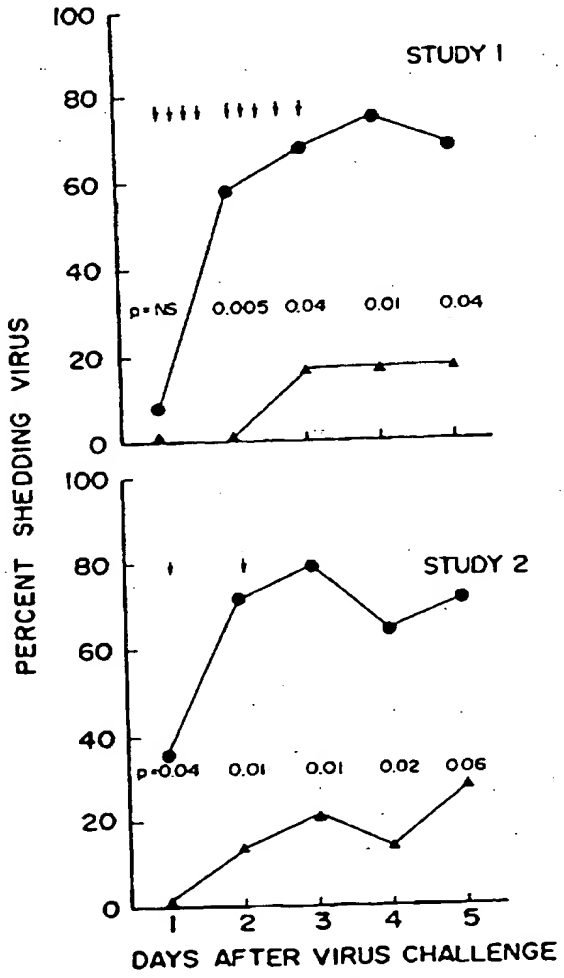

Figure 2. Rate of virus shedding in IFN- (▲) and placebo-treated (●) volunteers after experimental rhinovirus type 39 challenge. The significance of differences between IFN and placebo recipients was determined by two-tailed Fisher's exact test on each postchallenge day.

Only one subject had a detectable level on the fifth day. In the second study, in which nasal washes were collected at 22–24 hr after the preceding drug administration, geometric mean nasal wash IFN concentrations were 21, 40, 34, and 3 IU/ml on the corresponding days. Of 180 nasal wash specimens collected from placebo-treated, virus-exposed volunteers, nine samples contained detectable IFN in concentrations ranging from 7 to 707 IU (geometric mean, 27 IU). In the second study, sera obtained 24 hr after the last drug dose had no detectable IFN activity.

Infection rates and virus shedding. The infection rates determined by virus isolation and/or fourfold or greater rises in homotypic serum neutralizing antibodies are listed in table 1. The efficacy of IFN-α2 in preventing infection determined by either criterion was 78% ($P < 0.02$) in the first trial and 45% ($P = 0.12$) in the second. Approximately three-fourths of placebo recipients in either study shed virus. The efficacy of IFN-α2 in preventing virus shedding was 78% ($P < 0.02$) in the first study and 64% ($P < 0.03$) in the second.

The daily frequency of virus shedding was markedly reduced in the IFN groups in both studies (figure 2). As detailed in table 1, IFN-α2 administration was associated with an 82% reduction in the overall proportion of virus-positive days in the first study ($P < 10^{-6}$) and a 76% reduction in the second ($P < 10^{-6}$). Furthermore, on both the fourth and fifth days after virus challenge, when IFN concentrations in nasal washes were negligible or absent (figure 1), the proportion of IFN recipients who shed virus was significantly lower than that of placebo recipients in both

Table 2. Occurrence of colds and measurements of illness following exposure to rhinovirus type 39 in placebo- and IFN-treated volunteers.

Study	Treatment	No. with colds/ total no. exposed (%)	No. with colds and infection/ total no. exposed (%)	Nasal mucus weights (g/5 days)*	Symptom score (5 days)*
1	Placebo	6/12 (50)	4/12 (33)	26.2 ± 6.3†	11 ± 4
	IFN	2/12 (17)	0/12	8.6 ± 2.1†	6 ± 1
2	Placebo	8/14 (57)‡	8/14 (57)‡	60.1 ± 17.9‡	15 ± 4‡
	IFN	2/14 (14)‡	2/14 (14)‡	13.6 ± 4.0‡	3 ± 1‡

NOTE. Infection was determined by virus isolation and/or development of fourfold rise in serum neutralizing antibody to challenge virus.

* Data are means ± SEM.

† $P < 0.02$ (placebo vs IFN group).

‡ $P < 0.05$ (placebo vs IFN group).

studies (figure 2). Overall, 36 (69%) of 52 specimens from placebo recipients were virus-positive on these two days, compared to nine (17%) of 52 specimens from IFN recipients ($P < 10^{-6}$).

Illness rates and nasal mucus weights. In the first study, four of 12 placebo and none of the IFN recipients had colds and laboratory documented infection (table 2). Two additional subjects in each group met the criteria for a cold but did not have laboratory evidence of infection. In the second study, eight of 14 placebo and two of 14 IFN recipients had colds ($P < 0.05$), all of which occurred in association with laboratory-documented infection. Two of three asthmatic subjects who received placebo and two of four who received IFN-α2 had laboratory-documented infection. Only one of the placebo recipients developed a cold. Overall, 46% of placebo and 8% of IFN recipients had colds in association with infection ($P < 0.01$). The calculated efficacy of IFN-α2 in preventing colds documented to be secondary to RV infection was 100% in the first study and 75% in the second ($P < 0.05$).

In both studies, IFN-treated volunteers had significantly lower cumulative weights of expelled nasal mucus as compared to volunteers who received placebo (table 2). The mean daily weights of expelled nasal mucus are shown in figure 3. The treatment groups were similar on the day of virus challenge, but placebo recipients showed a rapid increase and subsequent peak in nasal mucus production on the second and third days after virus challenge. This pattern was not observed in the IFN recipients.

Illness rates and nasal mucus shedding weight in volunteers with documented infection. In the combined studies, two (25%) of eight infected IFN recipients developed colds, compared to 12 (60%) of 20 infected placebo recipients ($P = 0.21$). The total symptom scores (mean ± SEM) in infected volunteers tended to be lower in IFN-treated (5 ± 2) as compared to placebo-treated (16 ± 3) volunteers ($0.05 < P < 0.1$). Similarly, the cumulative weight of nasal mucus (mean ± SEM)

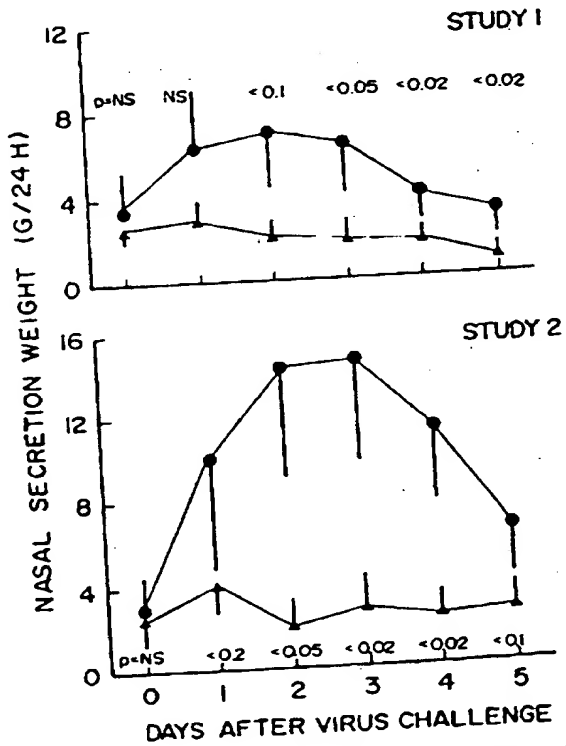

Figure 3. Comparison of daily nasal secretion weights (mean ± SEM) in IFN- (▲) and placebo-treated (●) volunteers after experimental rhinovirus type 39 challenge. The significance of differences between IFN and placebo recipients was determined by two-tailed Student's *t*-test on each postchallenge day.

in infected volunteers tended to be lower in IFN recipients (12.2 ± 3.3 g per five days) than in placebo recipients (52.7 ± 12.9) ($0.05 < P < 0.1$) and did not differ significantly from that of the 18 uninfected IFN recipients (10.9 ± 3.1) or eight (including two excluded from efficacy analysis) uninfected placebo recipients (14.2 ± 6.2).

Follow-up period. During the second week after virus challenge, all reporting subjects who had colds during the five-day postchallenge period continued to have upper respiratory tract symptoms. The mean duration into the second week was five days (range, two to seven days) in 14 placebo recipients and five days (range, three to seven days) in two IFN recipients.

Eight of 27 subjects who did not have colds during the five-day postchallenge period developed a URI with coryza during the second week after virus challenge. Six of 11 subjects (two of five IFN recipients and four of six placebo recipients) who had laboratory evidence of RV 39 infection reported a URI during the second week after challenge, as compared to two of 16 without infection (two of 12 IFN recipients; none of four placebo recipients) ($P < 0.05$).

Evaluation of side effects. As noted above, the mean cumulative weights of nasal secretions were similar in uninfected IFN and placebo recipients. The total symptom scores (mean ± SEM) in 18 uninfected IFN recipients were similar to those (3 ± 2) of eight uninfected placebo recipients. No fevers (oral temperature of ≥38.0 C) were noted in IFN recipients, nor did any recipient report systemic complaints, such as malaise or myalgia.

The frequency of symptoms immediately following intranasal delivery of the drug solutions was similar in the two treatment groups. Fifteen (54%) of 28 placebo recipients and 18 (67%) of 27 IFN recipients reported no symptoms. The most frequently noted symptoms were nasal irritation or burning (eight of 28 placebo recipients vs five of 27 IFN recipients) and sneezing (four of 28 placebo recipients vs five of 27 IFN recipients). Most symptoms were transient (<1 min) and mild, although two placebo recipients noted moderate burning with intranasal applications and one placebo and IFN recipient each reported moderate sneezing up to several minutes after one-half or more doses.

In the second study, the mean ± SEM change (mean percentage change) in leukocyte counts from the pretreatment values was $-0.5 \pm 0.3 \times 10^3$ leukocytes/mm^3 (−9%) in IFN recipients and $+1.3 \pm 0.4 \times 10^3$ leukocytes/mm^3 (+23%) in placebo recipients ($P < 0.01$). Three IFN recipients with normal leukocyte counts initially had leukocyte counts of 3.7, 3.4, and 3.8×10^3/mm^3 on testing 24 hr after the last IFN dose. All had leukocyte counts of $>4.0 \times 10^3$ leukocytes/mm^3 when retested two to three weeks later.

No other significant abnormalities or clinically important changes were noted in the results of hematologic, liver, or renal function tests or in those of routine spirometry. Levels of serum neutralizing antibody to IFN-α2 were below the limits of detectability (titer, <1:10) in all pretreatment and convalescent-phase samples.

Discussion

In the present study, intranasal application of IFN-α2, produced by recombinant DNA techniques, was effective in preventing both infection and illness following an experimental rhinovirus challenge. IFN administration was associated with a distinct antiviral effect as reflected in virus shedding patterns, whether administered prophylactically in multiple or once-daily treatments. While studies in nonhuman primates have found antiviral activity in experimental infection with vaccinia or encephalomyocarditis virus [5, 6], the present study conclusively demonstrates that bacterially produced IFN-α2 has significant antiviral activity in a susceptible human population.

Even in the IFN-treated volunteers who became infected despite treatment, objective and subjective measures of illness were comparable to those of uninfected placebo recipients and were substantially lower than those of infected placebo recipients. The proportion of virus-positive days was significantly higher in infected placebo recipients (78%) than in infected IFN recipients (40%), which indicated an antiviral effect although not complete protection in these IFN-treated volunteers.

One particularly appealing feature of IFN antiviral activity is prolonged duration of effect after interaction of IFN with host cells. Earlier in vitro studies with HuIFN-α or HuIFN-β (fibroblast-derived HuIFN) demonstrated that a concentration-dependent antiviral effect was achieved

within minutes of IFN exposure of human fibroblasts or nasal epithelial cells [15, 16] and, in studies with nasal epithelial cells, that this effect persisted for at least 72 hr following removal of IFN. Greenberg et al found that significant in vitro antiviral activity persisted in nasal epithelial cell scraping obtained 18 hr, but not 24 hr, after in vivo exposure to cotton pledgets soaked with HuIFN-α [17]. Studies of vaccinia virus and herpes simplex virus infections in both animal models [18, 19] and humans [20, 21] have demonstrated that one-time administration of IFN, up to 24 hr prior to virus exposure, is associated with significant antiviral effects. In our second trial, we tested the feasibility of using once-daily intranasal IFN administration for the prevention of rhinovirus infection and found that this approach was also effective in reducing virus shedding and preventing clinical illness.

The relationship beween IFN concentrations in nasal secretions and the development of an antiviral state within cells of the respiratory mucosa is uncertain, in part because IFN activity depends on specific binding to cell membrane receptors. In earlier studies, in which an antiviral effect was not documented, mean IFN concentrations ranged from 280 IU/ml to >500 IU/ml of nasal wash collected after intranasal administration of 10^6 IU (at 1 hr) [3] or 7.5×10^6 IU (at 2 hr) [4], respectively. In our first trial, we found comparable concentrations of residual IFN (figure 1) in nasal wash samples collected at 8–9 hr after the preceding dose. Much lower IFN concentrations were found in nasal washes of IFN recipients in the second study, but washes were collected at 22–24 hr after the preceding dose. The nasal wash IFN concentrations (geometric mean ± SEM) in samples collected from six infected IFN recipients (6 ± 3 IU/ml of nasal wash) on the first and second days after virus challenge were significantly lower than the corresponding concentrations (91 ± 3 IU/ml) in eight uninfected IFN recipients ($P < 0.001$). Whether the infected IFN recipients differed from the uninfected ones in their nasal clearance of IFN was not directly studied, but the results suggest that variability in nasal clearance of IFN among individuals may have been related to differences in infection rates.

We do not feel that residual IFN in nasal wash specimens interfered with the recovery of virus in cell culture. In earlier studies [11], we determined that IFN-related inhibition of RV CPE could be avoided by incorporation of antibody to IFN in the collection broth and by repetitive washing of the monolayers after adsorption of sample. Both of these techniques were used in the present study for processing specimens. Furthermore, significant differences in virus shedding rates persisted between IFN and placebo recipients on days when IFN concentrations were low or absent in nasal washings.

In the present study, intranasally applied IFN-α2 was well tolerated during short-term administration. In contrast to an earlier study of purified HuIFN-α in which mild local side effects were reported [4], we did not find subjective or objective evidence of local toxicity as compared to the placebo vehicle. However, reversible leukopenia was observed in several IFN recipients. The possibility that intranasally applied IFN could lead to systemic absorption sufficient to cause hematologic side effects needs further study.

The results of the present study suggest that use of IFN-α2 may meet the expectations of being a safe and effective means of preventing the common cold. Given prophylactically in the present study, IFN-α2 dramatically reduced the infection rate following RV challenge. However, since we performed virus cultures for only five days after virus challenge, we cannot exclude the possibility that IFN administration may have merely delayed the onset of virus shedding or illness in some recipients. Samo et al [22] observed a late increase in virus shedding but not illness in RV type 13–infected volunteers treated with recombinant leukocyte A IFN (10×10^6 IU per day). It remains to be determined whether long-term intranasal administration of IFN-α2 will be safe and well tolerated or if IFN-α2 will be useful in the treatment of established colds.

A practical application for the use of IFN-α2 would be its prophylactic use by members of a family in which a member had developed a new cold, since intrafamilial spread is an important route of RV transmission [23]. Alternative target groups who are at increased risk for respiratory complications of rhinovirus infection include asthmatics [23, 24] and those with chronic lung disease [25]. The present study provides preliminary evidence to indicate that intranasal IFN-α2 could be safely used in asthmatic patients. Field trials of intranasal IFN-α2 in natural rhinovirus

and other respiratory viral infections are warranted.

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